In the claims:

34. (Amended) Isolated nucleic acid encoding [the antibody of claim 1] a humanized anti-VEGF antibody which binds human VEGF with a K_d value of no more than about 1 x 10^{-8}M.

Remarks

Claims 34-38 are under consideration in this case. An Appendix with the claims as pending is attached for the Examiner's convenience. Claim 34 has been re-written to be in independent form, as a result of the restriction requirement. As this claim has already been considered in its independent form, no new issues are raised by this amendment.

As requested, the status of Serial No. 08/833,504 has been incorporated into the specification. While this application does not technically claim priority to it since it was filed on the same day, for the record, Serial No. 09/056,161 which is a continuation of Serial No. 08/833,504, was filed April 6, 1998.

Applicants filed an Information Disclosure Statement on January 30, 1998, and on October 26, 1998. Applicants request that the Examiner review the art and send Applicants the Forms 1449 showing the Examiner's initials indicating that the art has been considered. Of note, Applicants have received the initialed Form 1449 for the Information Disclosure sent on March 20, 1998.

Rejections under 35 U.S.C. Section 103

Claims 34-38 are rejected under 35 U.S.C. Section 103 as being unpatentable over WO 94/10202 (Ferrara). Applicants respectfully traverse.

To render an invention obvious, the prior publications must (1) disclose all of the claimed elements of the invention and (2), provide a reasonable expectation of success in arriving at the claimed subject matter.

Ferrara discloses anti-VEGF monoclonal antibodies; one murine anti-VEGF monoclonal antibody, A4.6.1, has a binding affinity of 1.2 x 10^9 liters/mole and the other murine anti-VEGF monoclonal antibody, B2.6.2, has a binding affinity of 2.5 x 10^9 liters/mole (page 20, lines 23-24). Additionally, Ferrara discloses that humanized forms of

the anti-VEGF antibodies can be formed.

Applicants submit that the skilled artisan would not have a reasonable expectation of success from Ferrara alone that one could form a humanized form of the murine anti-VEGF antibody of Ferrara that would have a binding affinity of within ten-fold of the murine antibody, as claimed.

Applicants point to their own initial results of forming a humanized anti-VEGF antibody, "hu2.0" discussed on page 63, lines 10-18. Hu2.0 was formed by grafting CDRs from murine A4.6.1 onto a human framework. The binding affinity of hu2.0 was greater than 7 μM, or 7 x 10^{-6} (line 17 and Table 1 of page 66) whereas as discussed above, Ferrara discloses a murine antibody having a binding affinity of around 1.2 nM, or 1.2 x 10^{-9}. Thus, the binding affinity of the initial humanized antibody had significantly greater than a 1000 fold reduction in affinity over the murine antibody.

While the skilled artisan might have tried to improve the binding affinity of the humanized antibody by making individually selected substitutions in the framework, the skilled artisan would not have expected to increase the binding affintity of 7 x 10^{-6} to the extent of the presently claimed antibodies.

The present invention provides for the first time the unexpectant result of a humanized antibody for VEGF having a binding of affinity of no more than 1 x 10^{-8}. To achieve this result, a number of methodologies were uniquely combined for the first time. For example, the present invention includes the utilization of a phagemid library and phage display to produce a rapid and efficient system of identifying antibodies having desirable binding affinities, wherein the desirable antibodies are selectively enriched. The system has been modified such that randomization of the amino acids was widely distributed (see page 64, lines 14-28). Moreover, the system of the present invention selectively enriches the tightest binding clone (page 66, line 15). Additionally, cumulative combination of mutations were used to enhance the affinity of a humanized anti-VEGF antibody, see page 67, lines 28-30. Using this unique system, for the first time antibodies to VEGF having binding affinities which fall within the scope of the claimed subject matter are provided, see page 79, Table 15.

In review, prior to the present invention, the skilled artisan would not expect to arrive at the claimed subject matter. As demonstrated in the application, the initial humanized antibody had a binding affinity of 7 x 10^{-6}, page 66, Table 7. While the skilled artisan may have made minor individual adjustments to such an antibody, the skilled artisan would not have expected to arrive at an antibody that had a binding affinity which was not

greater than about 1 x 10^{-8}. The present disclosure provides, for the first time, the surprising results of a humanized antibody for VEGF having the claimed binding affinity.

Since the prior art must provide a reasonable expectation of arriving at the claimed subject matter, and because Ferrara does not provide this, as demonstrated in the present application, Applicants submit that Ferrara does not render the present invention obvious. Applicants therefore request that the rejection be withdrawn.

For all the foregoing reasons, Applicants submit that the claims are in condition for allowance and earnestly solicit allowance of such claims. If there are any remaining issues, Applicants respectfully request the Examiner to call the undersigned, Dolly Vance, at 415-781-1989.

Respectfully submitted,

Dated: 1/28/99

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